REMARKS

Claims 1 and 5 have been amended. Claims 1-8 are now pending in this application. Claims 5 and 6 are withdrawn from consideration.

Support for the amendment to claim 1 is found in the existing claims and the specification. In particular, the Examiner's attention is directed to the specification at page 4, lines 9-23; page 8, lines 4-7; and page 9, lines 15-18. Claim 5 has been amended to be commensurate in scope with claim 1. Rejoinder of claims 5 and 6 upon indication of allowable subject matter for claim 1 is respectfully requested.

Accordingly, the amendments do not constitute the addition of new matter. Applicant respectfully requests the entry of the amendments and reconsideration of the application in view of the amendments and the following remarks.

Interview

Applicants thank Examiner Goldberg for the courtesy of a personal interview with the undersigned and Dan Altman on October 13, 2006. The interview is summarized on page 4.

Rejection under 35 U.S.C. § 102(b) (Fodor)

Claims 1-4, and 7-8 are rejected under 35 U.S.C. § 102(b) as being anticipated by Fodor, et al. (US Application No. 2001/53519).

Fodor teaches oligonucleotide arrays which include every 10-mer which would inherently include the capture probes of Applicants' claimed invention.

This ground of rejection is addressed by amendment of claim 1 to recite "said capture probes consisting of multiple pairs of capture oligonucleotides wherein the capture oligonucleotide pairs consist of (a) an oligonucleotide consisting of a nucleotide sequence complementary to or identical to a nucleotide sequence corresponding to the target sequence in which all of C's other than C's in all CpG dinucleotides… are replaced with T's and comprising a plurality of CpG dinucleotides and (b) an oligonucleotide consisting of a nucleotide sequence complementary to or identical to a nucleotide sequence corresponding to the target sequence in which all of C's are replaced with T's immobilized thereon…". The claims are thus limited to a specific subset of capture oligonucleotides which are not taught by Fodor. Accordingly, it is respectfully submitted that Fodor does not anticipate claim 1 as amended.

In view of Applicants' amendments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 102(b) (Berlin)

Claims 1, 3, and 8 are rejected under 35 U.S.C. § 102 (b) as anticipated by Berlin (WO 01/38565) as evidenced by Berlin (US 6,936,419).

Reference is made to the English language equivalent of WO 01/38565 which is US 6,936,419.

Berlin teaches arrays for the detection of cytosine methylations in genomic DNA. Berlin teaches oligomer arrays in which at least 75% of the oligomers comprise at least one sequence of the general formula DDCGDD or the general formula DDTGDD or the general formula HHCGHH or the general formula HHCAHH, where H represents A, C or T; and D represents A G or T.

It was previously argued that Berlin teaches a conventional array for detection of methylation in which each site is assayed individually with a collection of probes as shown in Figure 1. The Office Action counters that Berlin teaches that after amplification, different sequences bind to different sites on the oligomer array. The capture probes bind to different methylation sequences from the amplified product. The amplified products require adjacency between sequences which are interpreted as CpG islands.

In response, claim 1 has been amended to clarify that each member of the capture oligonucleotide pairs "comprise a plurality of CpG dinucleotides". Berlin teaches that a collection of probes assays for one methylated CpG dinucleotide, while the presently claimed invention teaches that the capture oligonucleotides pairs each correspond to a plurality of CpG dinucleotides from the target sequence. The presently claimed invention has the advantage that each potential methylation site does not need to be tested for individually. As shown in Figure 1 of the present specification, CpG's usually occur in islands. The CpG dinucleotide members of the islands are either all methylated or not (Figure 1B of the present application). In contrast, Berlin teaches that each possible CG must be tested (col. 4, line 66 to col.5, line 4).

Furthermore, as Berlin teaches testing of each CG with a separate combination of probes, Berlin does not teach any capture probe in which all CpG's are converted to TpG's. This differs from the present claims where the "b" oligonucleotide is defined as "(b) an oligonucleotide consisting of a nucleotide sequence complementary to or identical to a nucleotide sequence corresponding to the target sequence in which all of C's are replaced with T's immobilized thereon and comprising a plurality of CpG dinucleotides". The arrays of Berlin would not include the oligonucleotides as described and claimed. Furthermore, Berlin teaches an array with 1-4 possibilities (Figure 1 and col. 5, lines 21-67) as opposed to the amended claim 1 which specifies a pair of oligonucleotides to determine the presence of "a plurality of CpG dinucleotides", that is, a CpG island. Accordingly, Berlin does not teach all of the elements of the present claims.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 102(e) (Garner)

Claims 1, 3, and 8 are rejected under 35 U.S.C. § 102 (e) as being anticipated by Garner, et al. (US Publ. No. 2003/0152950).

The Office Action states that the claims are drawn to analysis of one or more CpG sites and Garner, et al. teach that many different CpG sites may be simultaneously queried with an array of many oligonucleotide probes (Office Action of 20060822, page 8, last three lines). The Examiner points out that the claims do not distinguish between Situation A:

________________X________________X________________
________________X________________X________________

and Situation B:

________________X_________
__________X________________

Garner, et al. teaches situation B. That is, CpG dinucleotides are individually tested for methylation of cytosine. Garner, et al. teach that "every base is queried" (paragraph 0060) and that "additional position query probe partners may be required if multiple CpG islands are on one probe. In this case every possible combination of methylations sites from the parent probe must be created" (paragraph 0061). The method of Garner, et al necessitates the generation of a large number of probes for each potential methylation site. Garner, et al. teach that if multiple CpG islands are on one probe, then "additional query partners...for every combination of methylation sites from the parent probe must be created". In contrast, Applicants teach situation A in which the capture oligonucleotides include more than one CpG dinucleotide. With the oligonucleotide–immobilized substrate of Applicants, a pair of capture oligonucleotides are used to query a CpG island with a plurality of CpG dinucleotides. Consequently, methylation can be detected using fewer probes.

The claims have been amended to clarify that Applicants' invention pertains to situation A. Claim 1 as amended clarifies that each capture nucleotide has a plurality of CpG's. Each member of the capture oligonucleotide pairs "comprise a plurality of CpG dinucleotides". The presently claimed invention has the advantage that each potential methylation site does not need to be tested for individually. This differs from Garner, et al. which teach that each CpG must be considered separately as discussed above. In the presently claimed invention, the multiple pairs for each CpG as taught by Garner, et al. can be replaced with a single pair which tests for a CpG island. It is respectfully submitted that Garner, et al. do not teach the invention as presently claimed.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a) (Berlin & Fodor)

Claims 2, 4, and 7 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Berlin (WO 01/38565) as evidenced by Berlin (US 6,936,19) in view of Fodor (US Application No. 2001/0053519).

Both Berlin and Fodor have been discussed above and that discussion is incorporated here. For the reasons given above, neither Berlin nor Fodor, taken separately or together, teach or suggest all of the elements of the invention as now claimed.

As discussed above, the claims have been amended to clarify that each member of the capture oligonucleotide pairs "comprise a plurality of CpG dinucleotides". It was Applicants' discovery that it is not necessary to test each possible methylation site, each CpG dinucleotide, individually. Rather arrays can be designed as presently claimed that assay for CpG islands which include a plurality of CpG dinucleotides. This is contrary to the teaching of the prior art as represented by Berlin. Berlin teaches arrays where methylation is detected using a collection probes which test for possible methylation at each site individually. That is, in the case of adjacent CpG dinucleotides, Berlin teaches a separate query for each dinucleotide while the presently claimed array is designed to detect a group of methylated CpG's.

Fodor does not correct this deficiency. Fodor is not directed to detection of methylation. Fodor teaches arrays which include all possible 10-mers. Accordingly, claim 1 is patentable over Berlin in combination with Fodor.

As claims 2, 4, and 7 depend from claim 1 which is neither taught nor suggested by Berlin taken with Fodor as discussed above, claims 2, 4, and 7 are patentable over the cited references at least for the reasons given above.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a) (Garner & Fodor)

Claims 2, 4, and 7 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Garner, et al. (US Publication No. 2003/0152950) in view of Fodor, et al. (US Application No. 2001/0053519).

Garner, et al and Fodor have been discussed above and this discussion is incorporated here. As discussed above, Garner, et al. teach that each CpG must be considered separately and that every possible change at a particular position must be queried (see paragraphs 0060-0062). This differs from the presently claimed invention which is based upon the unexpected discovery that all CpG's within an island are either methylated or unmethylated. The multiple probes for each CpG as taught by the references can be replaced with a single pair for a CpG island. As discussed above, the claims have been amended to clarify that each member of the capture oligonucleotide pairs "comprise a plurality of CpG dinucleotides". Accordingly, Garner, et al. do not teach or suggest the presently claimed invention.

Fodor does not correct the deficiencies of Garner, et al. Fodor is not directed to detection of methylation. Fodor teaches arrays which include all possible 10-mers. Accordingly, claim 1 is patentable over Garner, et al. in combination with Fodor.

As claims 2, 4, and 7 depend from claim 1 which is neither taught nor suggested by Garner, et al. taken with Fodor as discussed, claims 2, 4, and 7 are patentable over the cited references at least for the reasons given above.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

CONCLUSION

In view of Applicants' amendments to the claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: Oct. 25, 2006

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